Mechanisms of the Gewald synthesis of 2-aminothiophenes from elemental sulfur

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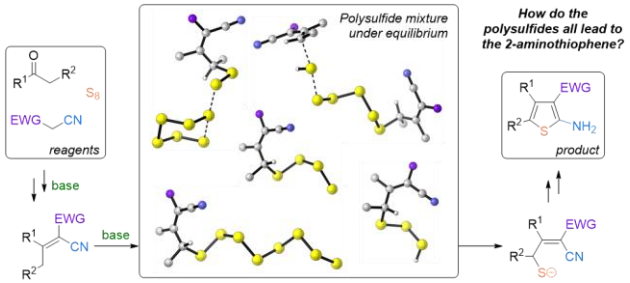

Abstract

The Gewald reaction is a well-established one-pot method to access 2-aminothiophenes from carbonyl compounds, activated acetonitriles, and elemental sulfur. To elucidate the reaction's poorly-understood mechanism, with regards to the decomposition of sulfur and polysulfide intermediates, we have performed a comprehensive computational study using Density Functional Theory (DFT) calculations at the M06-2X (or ωB97X-D)/aug-cc-pV(T+*d*)Z/SMD(C_2H_5OH) level of theory. The results show that the reaction is initiated by a Knoevenagel-Cope condensation, followed by opening of the elemental sulfur, leading to polysulfide formation. The polysulfide intermediates can interconvert and decompose using various mechanisms including unimolecular cyclization, nucleophilic degradation, and scrambling. Protonation of the polysulfides changes their electrophilic behavior and provides a kinetically favorable pathway for their decomposition. This protonation-induced intermolecular degradation is feasible for polysulfides of all lengths, but unimolecular decomposition is kinetically favored for long polysulfides (>5 sulfur atoms). None of the pathways provide any thermodynamic benefit due to the lack of resonance-stabilized leaving

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group, and a complex equilibrium of polysulfides of all lengths is expected in solution. Cyclization of the monosulfide with aromatization to the thiophene product is the only driving force behind the reaction, funneling all of the various intermediates into the observed product in a thermodynamically-controlled process.

Introduction

Elemental sulfur is a highly favored source of sulfur atoms in organic synthesis owing to its abundant availability and cost-effectiveness. It has found extensive usage in the creation of sulfur-based heterocyclic compounds and other organic reactions.[1, 2] Among the various types of heterocyclic compounds known for their unique structures, 2-aminothiophenes have attracted considerable attention due to their diverse and significant applications in pharmaceutical chemistry. Their incorporation into a molecule can lead to a wide range of biological activities.[3-5] (including antiproliferative, antiviral, antifungal, and antibacterial) There are various methods for the synthesis of 2-aminothiophenes,[6, 7] and among those the Gewald reaction appears as one of the most efficient approach to a variety of substituted 2-aminothiophenes. First reported in 1962,[8-11] the Gewald reaction has been used productively since and has four distinct iterations, each offering unique advantages.[6, 12-15] These iterations include: (i) the condensation of α-mercaptoketones or aldehydes with α-activated acetonitriles, in the presence of a basic catalyst like triethylamine or piperidine in ethanol, *N*,*N*-dimethylformamide (DMF), dioxane or water at 50 °C; (ii) a one-pot multicomponent reaction of carbonyl compounds with α-activated acetonitriles and elemental sulfur in the presence of amines such as diethylamine, morpholine, or triethylamine. Some of the key nitrile components include malononitrile, cyanoacetic esters, cyanoacetamides, and ω-cyanoacetophenones.[16] The preferred solvents are ethanol, DMF, dioxane, or neat for some carbonyl compounds; (iii) a two-pot reaction that involves an α-β-unsaturated nitrile (Knoevenagel-Cope condensation product) with elemental sulfur and (iv) an improved version of (i) involving the cyclization of α-activated nitriles with dimers of α-mercaptoketones or aldehydes.

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The *second version* of the Gewald reaction, a one-pot four-component procedure, stands out as the simplest and most efficient iteration. However, its reaction mechanism remains a mystery, prior to the formation of the key intermediate **[A]**, from which cyclization is believed to occur (**Figure 1)**. Gewald initially proposed that the enolate from the activated carbonyl compound would initiate the opening of S_8, generating an enolate polysulfide **[B]** that would decompose to the α-mercaptoketone of version (i).[8, 10] However, as the yields for a given thiophene are similar when versions (ii) or (iii) are used,[16] another hypothesis is that the Knoevenagel-Cope condensation happens first, and the α,β-unsaturated nitrile, which can be deprotonated by the amine base, leads to the opening of the sulfur ring, formation of polysulfide **[C]**, then intermediate **[A]** upon further decomposition.[6] Some reviews have completely avoided discussing the steps between **[C]** and **[A]**, instead proposing a direct cyclization of **[C]**'s sulfenyl sulfur on the nitrile.[13, 14, 17] Some scientists have also proposed for this or similar transformations that sulfur needs to be activated before the deprotonated α,β-unsaturated nitrile can attack it, with the amine acting as a nucleophile and resulting in ammonium polysulfide **[D]**.[18-20] Due to the transient nature of polysulfide intermediates, obtaining experimental evidence for any of these intermediates is challenging at best. As part of our group's ongoing investigation into the mechanisms of elemental sulfur and polysulfides,[21, 22] we have undertaken a study of the Gewald reaction using DFT calculations. We now report a comprehensive study of the competing mechanisms, elucidating which species is responsible for opening of the elemental sulfur and identifying the various pathways that account for the formation of 2-aminothiophene from the organic polysulfide that is initially generated.

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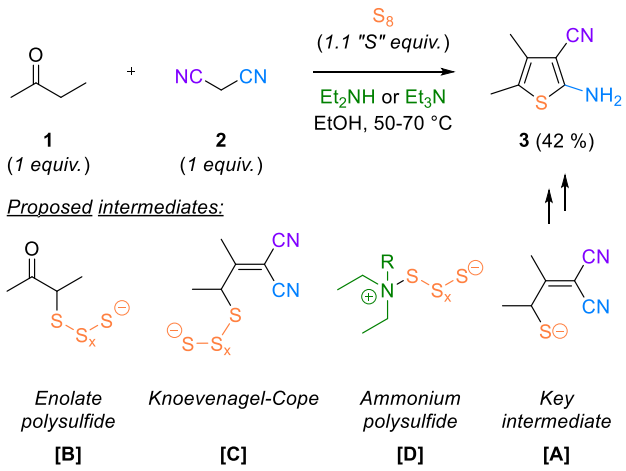

Figure 1: Plausible intermediates in the Gewald reaction of substrates **1** and **2**.

Computational Methodology

All of our Density Functional Theory (DFT) calculations were conducted using Gaussian 16, and we employed the ωB97X-D/aug-cc-pVDZ[23] level of theory to optimize the geometries of all reactants, transition structures (TSs), intermediates, and products. We selected this functional due to its proven effectiveness in previous investigations by us and others into the reaction of polysulfides with nucleophiles.[21, 22, 24-26] We accounted for solvation effects using the SMD solvation model,[27] which is appropriate for polar solvents such as ethanol, a representative solvent commonly used in such transformations. Single-point energy refinements were then obtained with the ωB97X-D and M06-2X functionals and the triple-zeta tight-d-augmented basis set aug-cc-pV(T+*d*)Z, necessary to obtain accurate energies for sulfur compounds.[28] Both functionals (ωB97X-D, M06-2X) agree on the conclusions of the study (see Table S1), and the results reported in the main text are derived from calculations conducted at the M06-2X/aug-cc-pV(T+*d*)Z/SMD(EtOH) level of theory as they predict lower activation barriers that are more likely for the reaction temperature. All computational details are provided in the Supporting Information. To minimize the computational cost of our calculations, we selected butanone **1** and malononitrile **2** as model α-methylene carbonyl and activated nitrile compounds, respectively, while *N*,*N*-

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diethylamine was used as the amine base. This combination of reagents was reported by Gewald, providing the aminothiophene **3** in 42% yield.[10, 16] Importantly, only the methylene carbon is thiolated in this reaction as none of the isomeric 2-amino-3-cyano-4-ethylthiophene was detected.[6] The low yield is due to the undesired dimerization of the α,β-unsaturated nitrile which likely competes with its reaction with sulfur, an issue with malononitrile derivatives that is not as prevalent for other activated acetonitriles. These conditions are representative for type II Gewald reactions that can produce the 2-aminothiophenes in high yields.[17]

Results and Discussion

Role of amine base

We first investigated the likelihood of generating the various intermediates from **Figure 1**, examining the role of the Et_2NH base in the one-pot system, with regards to the three other reactants (**Figure 2**). Consistent with the pK_a of butanone (~20), diethylammonium (11) and malononitrile (11), we find that deprotonation at the 1- or 3-position of butanone by Et_2NH is unfavored by 23.5 or 23.1 kcal/mol, while deprotonation of malononitrile is endergonic by only 2.5 kcal/mol (**Figure 2A**). Intermediates **1a** and **1b** would be involved for the enolate polysulfide pathways, while intermediate **2a** is necessary for the Knoevenagel-Cope condensation (**Figure 3**). Otherwise, the amine could function as a nucleophile to open the octasulfur ring, yielding the ammonium-polysulfide $\mathbf{Et_2N^+H\text{-}S_8^-}$ ([D] in **Figure 1**). This pathway is highly unfavorable, with a reaction free energy of 34.9 kcal/mol (**Figure 2B**). The ammonium moiety of $\mathbf{Et_2N^+H\text{-}S_8^-}$ is predicted to be highly acidic, and its deprotonation by Et_2NH or by the terminal sulfide (which is poorly basic, see below) is exergonic by 16.9 or 13.0 kcal/mol, respectively generating $\mathbf{Et_2N\text{-}S_8^-}$ or $\mathbf{Et_2N\text{-}S_8H}$. Nonetheless, the opening of sulfur by Et_2NH is highly endergonic. Importantly, our calculations also show that other amine nucleophiles, such as DABCO and triethylamine, do not activate elemental sulfur favorably (**Figure 2C**). Indeed, nucleophilic activation of sulfur by amines is plagued by high reaction energies, indicating

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that ammonium polysulfides are unlikely to form, and should not be able to compete with malononitrile anion (**2a**) formation, the first step of the Knoevenagel-Cope condensation, as the most favorable route. As such, our calculations clarify that neither enolate polysulfides or ammonium polysulfides (**[B]** and **[D]** in **Figure 1**) are likely to be involved in the Gewald reaction.

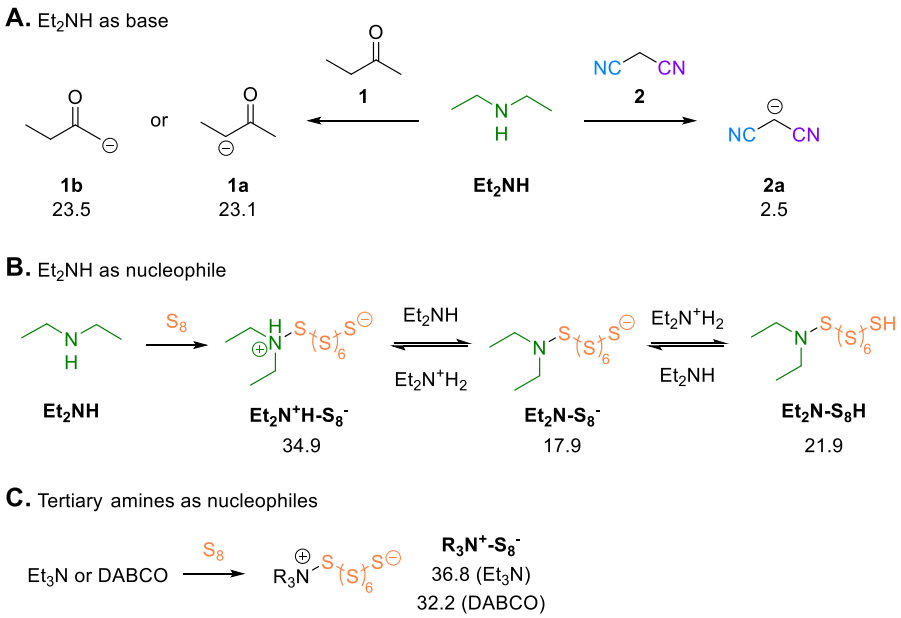

Figure 2: Reaction free energies (kcal/mol) for the possible roles of amines in the reaction.

Knoevenagel-Cope condensation

From the malononitrile anion (**2a**, **Figure 2**), Knoevenagel-Cope condensation can occur with butanone (**Figure 3**). Our calculations indicate that the condensation require an activation energy of at least 21.7 kcal/mol, forming the alkoxide intermediate **4a** with a 20.3 kcal/mol reaction free energy. **4a** can easily access alcohol **4** by proton transfer, releasing 16.4 kcal/mol. Moreover, dehydration of **4** is favorable by an additional 9.2 kcal/mol, ultimately yielding the final product of the Knoevenagel-Cope condensation (**5**). Formation of this product is exergonic by 5.4 kcal/mol from **1** and **2a** and thus a likely intermediate in the Gewald reaction.

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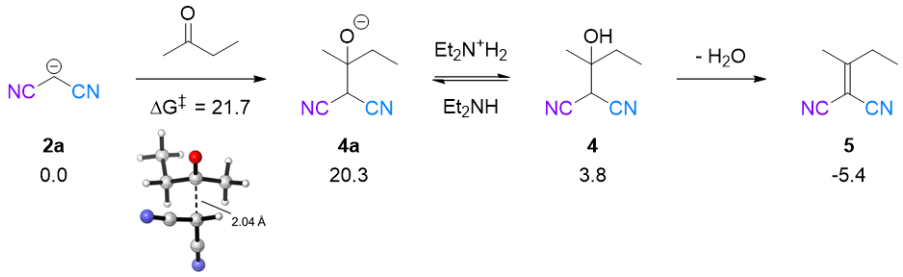

Figure 3: Formation of 2-(butan-2-ylidene) malononitrile (**5**) via Knoevenagel-Cope condensation from malononitrile anion (**2a**) and butanone **1**. Free energies (in kcal/mol) are relative to **1** and **2a**.

Sulfuration of the condensation product with elemental sulfur

In order for the Gewald reaction to proceed, intermediate **5** must get sulfurated either from elemental sulfur or an activated form thereof. Deprotonation at the γ position of the α,β-unsaturated malononitrile (**5**) by Et_2NH can result in two substituted allylic anions susceptible of acting as nucleophiles for the opening of S_8 (**Figure 4**). Of the two possibilities, the more substituted anion **5b** is favored over **5a** by 0.4 kcal/mol. **5b** also has a lower barrier for nucleophilic attack on S_8 (25.4 vs 27.2 kcal/mol) and the resultant polysulfide **5b-S_8^-** is more stable than its isomer **5a-S_8^-** by 2.3 kcal/mol. This is in line with the experimental results that isolated **3** as the sole thiophene product, without any trace of **6**. As the decomposition pathways of **5b-S_8^-** have similar activation free energies than attack of **5b** on S_8, it is unclear if this initial sulfur opening is the rate-determining step of the reaction.

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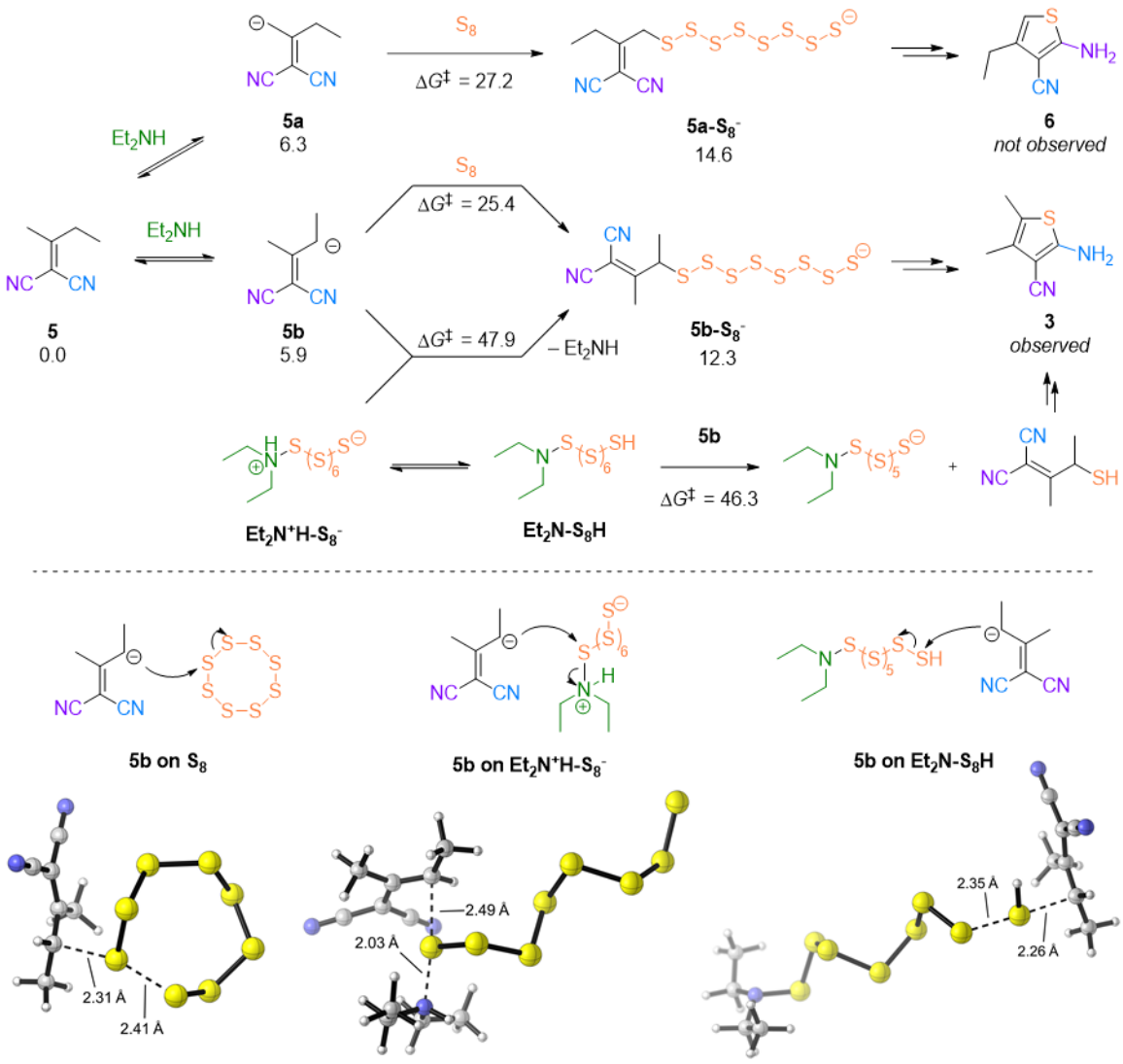

Figure 4: Sulfuration of deprotonated **5** with elemental sulfur or amine-activated forms. Free energy in kcal/mol and are relative to **5**, Et_2NH, and S_8.

A common hypothesis in the literature is that elemental sulfur is activated by an amine nucleophile prior to attack by the substrate. We tested this hypothesis directly, locating the TSs for attack of **5b** on the S^1 position of **Et_2N^+H-S_8^-** (exchanging the octasulfide chain from the amine to the carbon nucleophile) and for the abstraction of the terminal SH group of **Et_2N-S_8H** by **5b** (**Figure 4**). In the former case, the reaction only requires 7.2 kcal/mol of activation free energy from the preceding intermediates, however since **Et_2N^+H-**

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S_8^- lies 34.9 kcal/mol above Et_2NH and S_8, the total free energy needed from **5**, Et_2NH and S_8 is 47.9 kcal/mol (including 5.9 kcal/mol for deprotonation of **5**). Similarly, in the latter case the activation barrier is 18.6 kcal/mol but **Et_2N-S_8H** lies 21.9 kcal/mol above the reagents and thus the total free energy required is 46.3 kcal/mol. Overall, were these amine-activated forms of sulfur found in significant concentration in solution, our calculations predict that they should be competent for transferring sulfur atoms to the nucleophile **5b**; however, their free energies of formation are so large that their presence is unlikely under typical conditions for the Gewald reaction.

*Decomposition of polysulfide **5b-S_8^-** en route to the 2-aminothiophene*

Opening of elemental sulfur by **5b** leads to an octasulfide intermediate, yet the final product of the Gewald reaction is a 2-aminothiophene, which has only one sulfur atom in its skeleton. Since approximately 1/8th equivalent of S_8 is used during the reaction, all sulfur atoms have to be involved in thiophene formation and thus the decomposition of **5b-S_8^-** must occur through successive, productive pathways. Experimental evidence or kinetic studies regarding the degradation of such polysulfides and the formation of the requisite thiolates ([A] in **Figure 1**) are, to the best of our knowledge, still lacking. Limited attention has been devoted to these critical steps prior to our study of elemental sulfur decomposition by cyanide and phosphines.[22] In that study we compared four decomposition pathways: nucleophile attack, unimolecular decomposition, scrambling pathways (attacks of polysulfides on each other) and thiosulfoxide intermediacy. We found that for polysulfides that can produce good leaving groups (such as thiocyanate or phosphine sulfide), unimolecular decomposition is kinetically preferred over both nucleophilic attack and scrambling pathways, with the latter being also unlikely due to the low expected concentration of polysulfides given their reactivity. Thiosulfoxides (branched sulfur chains) are unstable isomers of polysulfides and as such should not be invoked in such reactions. In the case of the Gewald reaction, unimolecular cyclization has been proposed as the mechanism of polysulfide decomposition by Vinogradoff, Sabnis, and others.[13, 20, 29,

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[30] We thus compared the plausible pathways identified previously toward the decomposition of **5b-S$_8^-$** (**Figure 5**).

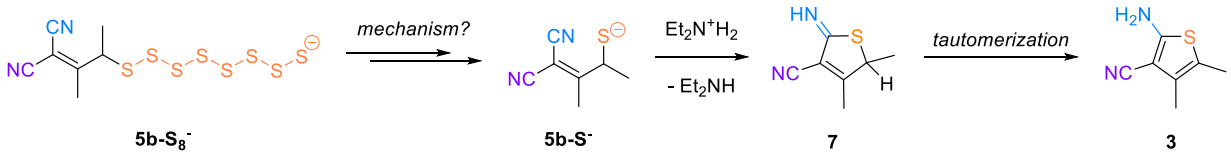

Figure 5: Key questions for the mechanism of the Gewald reaction

Unimolecular decomposition through cyclization

The first plausible decomposition pathway of intermediate **5b-S$_8^-$** is through intramolecular cyclization (**Figure 6A**). This route involves ring-closing nucleophilic attack from the terminal sulfide anion, generating (poly)sulfides and the corresponding cyclic sulfur allotropes. Barriers for those cyclizations are low and easily accessible at the reaction temperature, with intramolecular attack at S^2 (leading to S_7 and the desired monosulfide **5b-S$^-$**), S^3 (leading to S_6 and **5b-S$_2^-$**) or S^4 (leading to S_5 **5b-S$_3^-$**) requiring 17.7, 13.0 and 20.0 kcal/mol, respectively. Contrary to the unimolecular decomposition of cyano- or phosphonium polysulfides,[22] however, all cyclizations of **5b-S$_8^-$** and shorter polysulfides are endergonic or isoneutral, thus are all reversible. Unimolecular cyclization in the current system seems governed by the stability of the cyclic sulfur allotrope, since cyclizations that generate S_6 are the least thermodynamically disfavored (**Figure 6B-C**). Cyclic S_6 is known to be more stable in comparison to cyclic S_5, cyclic S_7, or other sulfur allotropes except S_8.[31] Although attack at S^3 on **5b-S$_8^-$** could be expected to be fast in solution due to its low activation free energy, it is an isoneutral reaction (ΔG_{rxn} = -0.1 kcal/mol), while cyclizations of shorter polysulfides become highly endergonic and display larger barriers, and thus are unlikely, as the polysulfide shortens. Any sulfur allotropes formed during unimolecular decomposition are predicted to be more reactive toward the nucleophile **5b** than S_8, ensuring their fast conversion to open polysulfides **5b-S$_x^-$** (Table S2).

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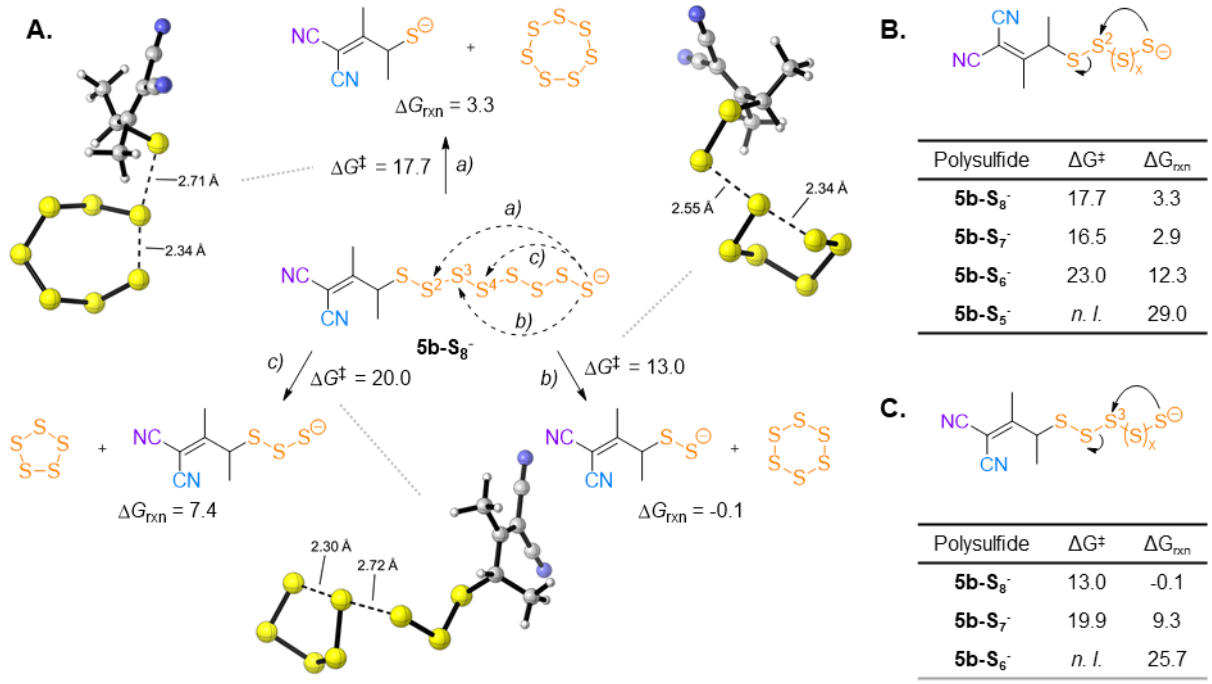

Figure 6: A) Unimolecular decomposition possibilities from **5b-S$_8^-$**; B) Cyclization of polysulfides through intramolecular attack at S^2; C) Cyclization of polysulfides through intramolecular attack at S^3. Free energies are in kcal/mol.

While cyclization at S^2 on any polysulfide generates **5b-S$^-$** that is necessary for thiophene formation (**Figure 5**), there is no thermodynamic incentive for this pathway in this system, when compared to $^-$CN and PMe$_3$ nucleophiles.[22] This change arises because the monosulfides from $^-$CN and PMe$_3$ (namely, $^-$SCN and $^-$S-$^+$PR$_3$) are excellent, resonance-stabilized leaving groups, accelerating their formation in comparison to longer polysulfide fragments. In contrast, the monosulfide **5b-S$^-$** lacks resonance stabilization and is more basic (a worse leaving group) than disulfide **5b-S$_2^-$**, itself more basic than longer polysulfides **5b-S$_x^-$**. The measured pK_a values of inorganic polysulfides in water (H_2S: 7.0, H_2S_2: 5.1, H_2S_3: 4.3, H_2S_4 – H_2S_8: 3.9 – 3.4)[32-34] and the increased acidity of alkyl persulfides (RSSH) versus their corresponding thiols (by 1-4 pK_a units)[35-37] match this conclusion. Overall, unimolecular cyclization is kinetically plausible mostly for long

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polysulfides, but does not provide a clear thermodynamic driving force towards the formation of the monosulfide that is needed for 2-aminothiophene formation.

Nucleophilic bimolecular degradation

Another plausible pathway for decomposition of **5b-S_8^-** or any shorter polysulfide would be bimolecular nucleophilic decomposition, where **5b** cleaves one of the various S-S bonds. Once again in contrast to cyano- or phosphonium polysulfides, we find that there is no kinetic or thermodynamic driving force for the decomposition of polysulfide **5b-S_8^-** by the carbon-based nucleophile **5b** (**Figure 7**). Indeed, the only thermodynamically favorable decompositions happen through attack at S^4 to S^6 in the monosubstituted approach (**Figure 7A**), releasing at most 1.8 kcal/mol. The Foss-Bartlett pathway (attack at S^2),[22] which would produce the desired monosulfide **5b-S^-**, is endergonic by 3.8 kcal/mol and thus reversible. Thermodynamically, the most favorable decomposition is through attack at S^5 (ΔG_{rxn} = -1.8 kcal/mol), leading to two tetrasulfides (**5b-S_4^-**). The tetrasulfide, in this system, appears to be the most stable polysulfide structure, followed by the tri- and pentasulfides. These results are in line with our discussion above, as none of the mono-, di-, or polysulfide products that are generated from decomposition of **5b-S_8^-** benefit from resonance stabilization of the sulfide anion that would favor a given structure. Once again, monosulfides are more basic and worse nucleofuges than di- or longer polysulfides, thus formation of mono- or disulfides is actually disfavored in the current system. Conversely, all attacks leading to the disubstituted (poly)sulfides are endergonic (**Figure 7B**), especially for attacks at S^3 through S^7 that produce short dianionic polysulfides.

Kinetically, none of the located pathways have low barriers that would compete with unimolecular decomposition or explain why 2-aminothiophenes are formed selectively in the Gewald reaction. Our calculations find that the most favored nucleophilic decomposition pathway of **5b-S_8^-** would be attack at S^2 in the disubstituted approach (**Figure 7B**, $\Delta G^{\ddagger}$ = 27.5 kcal/mol), but that attack is endergonic by 4.0

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kcal/mol and would generate a disulfide product that has not been reported in the reaction. In the monosubstituted approach, the Foss-Bartlett pathway has a large 31.5 kcal/mol activation barrier and it outcompeted by nucleophilic attack on S^3 or S^4 that have similar, lower barriers (29.0 vs 28.5 kcal/mol, **Figure 7A**). Attacks at these positions, however, lead to shorter polysulfides **5b-S$_y^-$** (y = 2-5) that eventually need to be decomposed further before obtaining the monosulfide **5b-S$^-$**, yet nucleophilic decompositions of shorter polysulfides through the Foss-Bartlett pathway are plagued by large activation barriers ($\Delta G^{\ddagger}$ = 31.4 – 39.3 kcal/mol) and by unfavorable thermodynamics (ΔG_{rxn} = 3.4 – 6.8 kcal/mol) (Table S3). As such, based on our current results, it appears unlikely that nucleophilic decomposition of **5b-S$_8^-$** or smaller anionic polysulfides by **5b** is a major decomposition pathway that explains the ready formation of **5b-S$^-$** or the 2-aminothiophene products in the Gewald reaction.

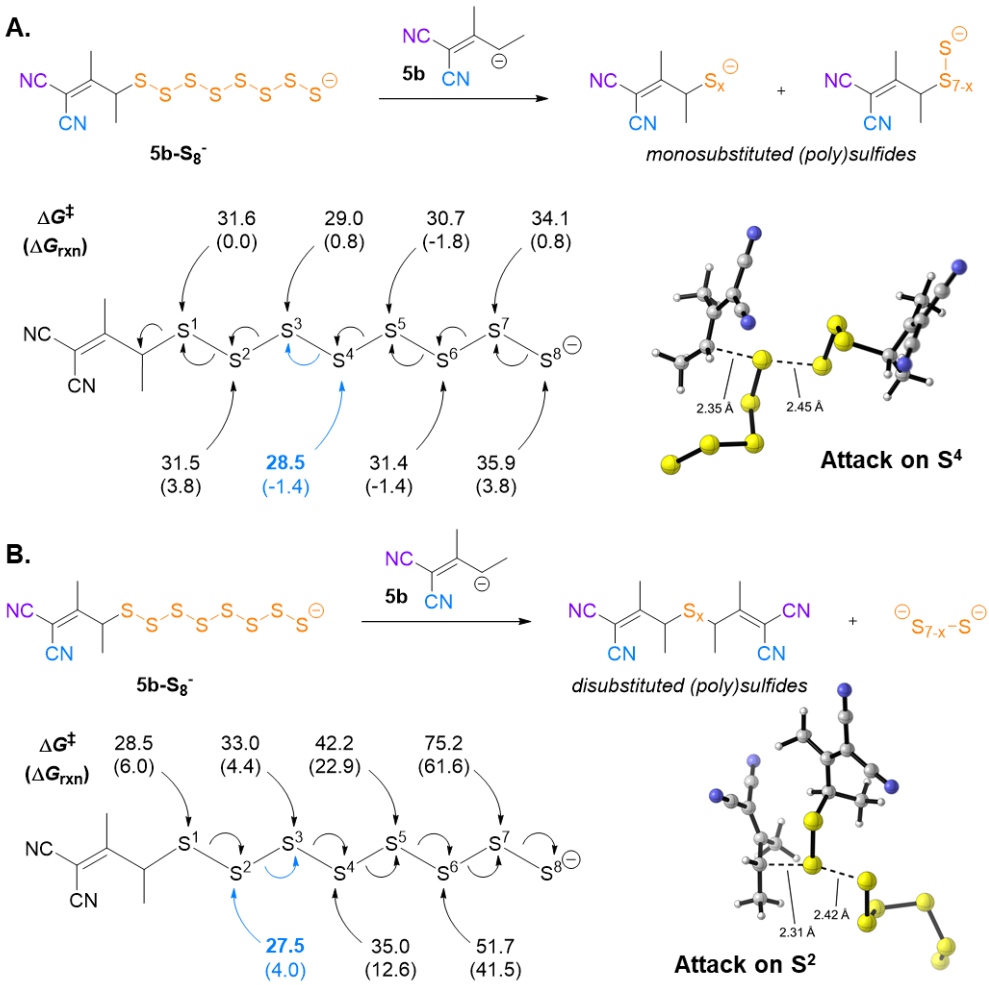

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Figure 7: Possible pathways for attack of **5b** on **5b-S_8^-** to form A) monosubstituted or B) disubstituted (poly)sulfides. Free energies of activation (free energies of reaction in parenthesis) are in kcal/mol.

Scrambling pathways

The results obtained from the unimolecular and bimolecular pathways above indicate that forming monosubstituted sulfide **5b-S^-** through decomposition of **5b-S_8^-** is not favorable either thermodynamically or kinetically, especially for short intermediate polysulfides. Another plausible pathway of polysulfide decomposition include "scramblings", where polysulfides act as nucleophiles to attack other polysulfides or sulfur allotropes, forming new polysulfides.[22] However, due to the lack of leaving group in **5b-S_y^-** as mentioned above, all of the scrambling reactions are endergonic and also lack a thermodynamic incentive (Table S4 and Scheme S1). Polysulfides are however competent nucleophiles for the opening of sulfur allotropes such as elemental sulfur (Scheme S2), although these reactions only generate additional polysulfides that still need to reach **5b-S^-** in order to form the thiophene product. Overall, as the polysulfides are high-energy intermediates (**Figure 10**) and thus present in minute concentrations, the rates of bimolecular scrambling reactions are expected to be low. Such pathways are thus unlikely to have a meaningful contribution in the Gewald reaction.

Protonation-induced intermolecular degradation of polysulfides

The results for the pathways explored above were not entirely satisfactory to explain the Gewald reaction, in particular the fate of short polysulfides. These need to be decomposed in order to use all sulfur atoms toward thiophene synthesis, but we could not locate plausible low-barrier pathways. In contrast to the reaction of sulfur with cyanide and phosphines, the Gewald reaction involves an acid-base equilibrium and a protic solvent. We thus wondered whether protonation of the polysulfides could provide a new reactivity paradigm explaining their decomposition to the monosulfide. Indeed, it has recently been appreciated that

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persulfides (RSSH) display nucleophilic or electrophilic behavior as a function of their protonation state, and that the terminal sulfur's electrophilicity increases upon protonation.[25, 38,39] Using $\mathbf{Et_2N^+H_2}$ as proton source, we compute that formation of **5b-S$_8$H** is endergonic by 4.4 kcal/mol, in line with the predicted acidity of long polysulfide species (see above) (**Figure 8**).

The electrophilic behavior of **5b-S$_8$H**, perhaps unsurprisingly, is at odds with that of its deprotonated form **5b-S$_8^-$**. While nucleophilic attack on **5b-S$_8^-$** yielded multiple plausible cleavage patterns, all with high activation free energies (> 27.5 kcal/mol, **Figure 7**), attack of **5b** on **5b-S$_8$H** is predicted to be fast and highly selective toward S^8 ($\Delta G^‡$ = 18.5 kcal/mol, 4.0 kcal/mol lower than any other cleavage), forming the thiol **5b-SH** and the heptasulfide **5b-S$_7^-$**. Internal cleavages of the polysulfide, whether toward monosubstituted or disubstituted polysulfides (for example HS$^-$ from attack at S$_7$, orange) are all kinetically and thermodynamically less favorable and thus unlikely to compete.

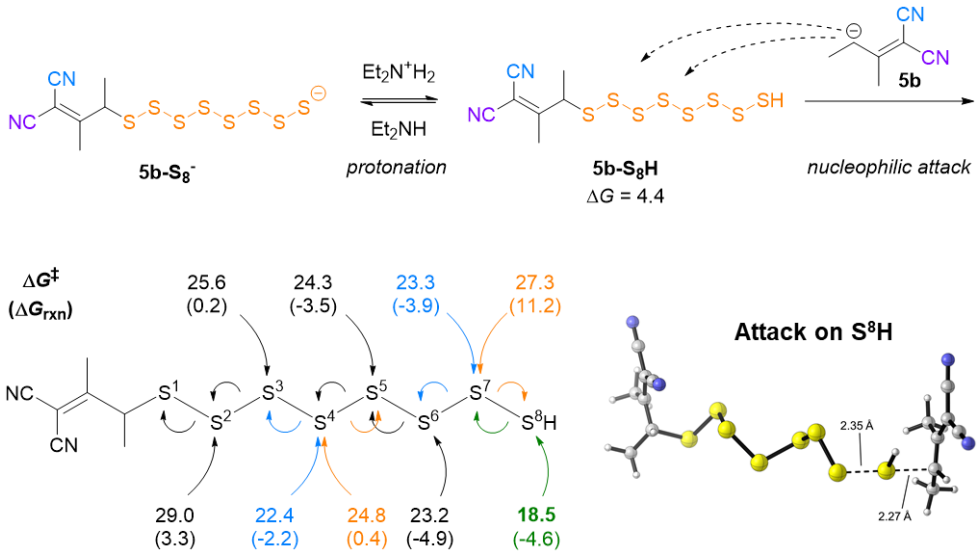

Figure 8: Decomposition pathways of **5b-S$_8$H** upon nucleophilic attack by **5b**. Free energies of activation (of reaction in parenthesis) are in kcal/mol and relative to **5b-S$_8$H** and **5b**.

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The specific reactivity of **5b-S_8H** provides a plausible pathway to access the monosulfide required for the Gewald reaction, since that reactivity is replicated in shorter polysulfides. Indeed, we studied the protonation energetics of shorter polysulfides and the activation barriers for nucleophilic attack of **5b** on those protonated polysulfides (**Table 1**). Multiple trends emerge from this data. First, protonation free energy is larger for longer than shorter polysulfides, which is in line with the greater acidity of the former as detailed above. There is a large change in acidity between the trisulfide and the pentasulfide, but smaller changes between longer polysulfides than the pentasulfide. On the other hand, nucleophilic attack on the terminal SH group of the protonated polysulfides is easier for longer polysulfides (18.6 kcal/mol for **5b-S_7H** versus 22.5 for **5b-S_2H**). This is also explained by the better leaving group ability of longer anionic polysulfides due to their lower basicity. When adding the nucleophilic attack barrier to the free energy of protonation, however, polysulfides of all lengths have similar total activation barriers, between 21.5 to 22.9 kcal/mol, indicating that this pathway is plausible for all polysulfides. Thermodynamically, formation of **5b-SH** using those pathways is slightly exergonic for longer polysulfides and slightly endergonic for shorter ones. This thermodynamic equilibrium is a constant of the Gewald reaction, as shown for the previously presented decomposition pathways. However, the protonation-induced decomposition shown here is unique in that the activation barriers are reasonable for 50-70 °C, and remain so even for short polysulfides, in sharp contrast to the previous hypotheses presented above. As such, this is the only plausible pathway we could find that explains the formation of eight monosulfide products from successive decomposition of polysulfides, starting with **5b-S_8^-**.

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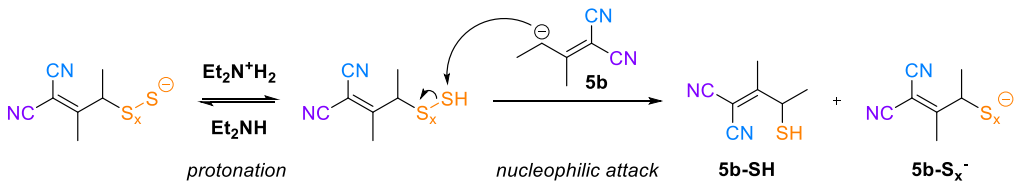
Table 1: Activation and reaction free energy (kcal/mol) for protonation-induced intermolecular degradation of polysulfides.



Polysulfide	x	$\Delta G_{protonation}$	$\Delta G^{\ddagger}_{Nu\text{-}attack}$	Total $\Delta G^{\ddagger}$	Total $\Delta G_{reaction}$
5b-S_8^-	7	4.4	18.5	22.9	-0.2
5b-S_7^-	6	3.9	18.6	22.6	-0.2
5b-S_6^-	5	3.9	18.5	22.3	-0.5
5b-S_5^-	4	3.7	19.2	22.9	0.7
5b-S_4^-	3	2.7	19.6	22.2	1.1
5b-S_3^-	2	1.0	20.5	21.5	1.8
5b-S_2^-	1	-0.3	22.5	22.3	2.8
5b-S^-	0	-3.9	-	-	-

Cyclization of monosulfide, disulfide, and trisulfide intermediates

From the above calculations, the degradation of polysulfides **5b-S_x^-** seems likely to proceed via unimolecular cyclization for long polysulfides ($x \geq 6$) and via protonation-induced bimolecular substitution for all lengths, rather than through nucleophilic attack on the anionic polysulfides or scrambling pathways. Due to the low or absent exergonicity of all those reactions, it appears that polysulfides of all lengths are under thermodynamic equilibrium in solution and complex mixtures can be expected. We thus wondered if cyclization and tautomerization of the short polysulfides might provide a thermodynamic driving force during the final steps of the Gewald reaction.

From the monosulfide **5b-S^-**, we find that cyclization of the sulfide anion on the nitrile, under general acid catalysis from diethylammonium, has a small activation barrier of 12.7 kcal/mol (**Figure 9A**),

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leading to dihydrothiophene **7** upon dissociation of diethylamine. Formation of this intermediate also releases 15.1 kcal/mol of free energy, providing a strong thermodynamic driving force. **7** can then tautomerize to the observed aromatic product, 2-aminothiophene **6**, releasing an additional 10.6 kcal/mol indicating that thiophene formation is the only irreversible step in the Gewald reaction. *A priori*, there is nothing preventing disulfide **5b-S_2^-**, trisulfide **5b-S_3^-**, or longer polysulfides, from forming their corresponding cyclic products. However, our calculations of those systems indicate that those cyclizations not only have larger activation barriers, but are also thermodynamically unfavorable. Indeed, **5b-S_2^-** requires 21.2 kcal/mol of free energy to cyclize with general acid catalysis, and the resulting intermediate **8** is only 0.5 kcal/mol lower in free energy, hinting at a reversible reaction (**Figure 9B**). Similarly, **5b-S_3^-** cyclization has a 24.3 kcal/mol barrier and the cyclic intermediate **9** sits 10.7 kcal/mol higher in free energy. Therefore, for any polysulfide except **5b-S^-**, cyclization and other reactions that result in exchanges between polysulfides are all under kinetic competition and under thermodynamic equilibrium. Once **5b-S^-** is formed, its lowest-barrier reaction pathway is for 2-aminothiophene formation, which upon completion releases 25.7 kcal/mol of free energy, at last trapping the three reagents (ketone, activated nitrile, and elemental sulfur) in their final product form.

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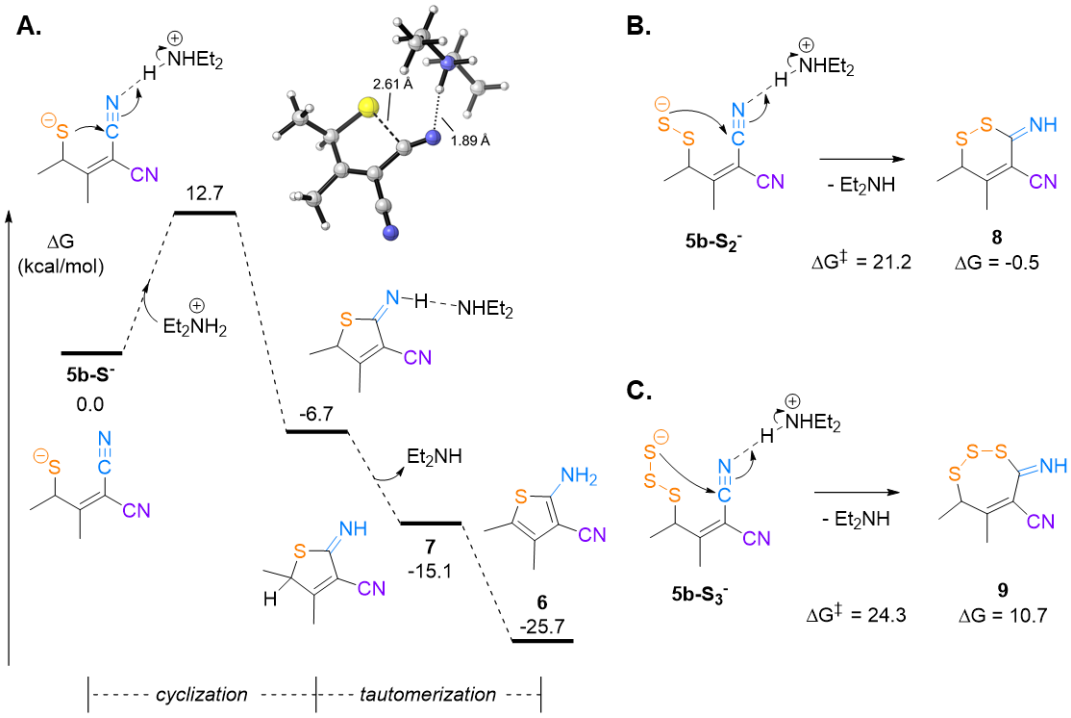

Figure 9: A) Cyclization and aromatization of monosulfide **5b-S**$^-$ under acid catalysis from $Et_2N^+H_2$; B) cyclization of disulfide **5b-S$_2$**$^-$; C) cyclization of trisulfide **5b-S$_3$**$^-$. Free energies are in kcal/mol and relative to the anionic (poly)sulfide and $Et_2N^+H_2$.

Complete Gewald reaction mechanism

Figure 10 illustrates the complete reaction pathway for the formation of 2-aminothiophenes in the one-pot Gewald reaction (version II). According to our calculations, the most likely initial step is the Knoevenagel-Cope condensation, where the deprotonated malononitrile anion and butanone react to form the condensation product **5**. This reaction has a barrier of 24.2 kcal/mol and is exergonic by 2.9 kcal/mol. Subsequently, deprotonation of **5** by Et_2NH yields **5b** as the major anionic species, which then opens S_8 with a 25.4 kcal/mol barrier (from **5**), forming **5b-S$_8$**$^-$ (+9.4 kcal/mol vs **1** and **2**). From this point, all related polysulfides are in equilibrium with each other and various decompositions are possible. Cyclization, protonation-induced nucleophilic decompositions, and scrambling reactions all can contribute to exchanges

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between polysulfides of various lengths that are of similar free energy (10.6 – 13.2 kcal/mol, vs 9.4 kcal/mol for **5b-S_8^-**). Of those mechanisms, cyclization is most likely for longer polysulfides, while protonation-induced decomposition is most likely for shorter polysulfides. For **5b-S_8^-**, two main pathways allow the formation of **5b-S^-** that is prerequisite for thiophene formation. First, direct cyclization (combined with opening of the S_7 allotrope by **5b**) requires at most 19.0 kcal/mol from **5b-S_8^-**. A second option is the protonation to **5b-S_8H**, allowing nucleophilic attack by **5b** to form **5b-SH** that can be deprotonated by Et_2NH. This path requires 22.9 kcal/mol from **5b-S_8^-**. Once **5b–S^-** is present in solution, however, its cyclization to the thiophene tautomer **7** only requires 12.7 kcal/mol, less than any "reverse" barriers to other polysulfides. **7** is only 1.1 kcal/mol higher in free energy than the reagents (**1** + **2** + S_8) and a thermodynamic sink for the polysulfide mixture. From **7**, tautomerization to the aromatic thiophene product **6** is exergonic (total ΔG = -9.6; -17.8 per thiophene when using all 8 sulfur atoms of S_8). In summary, there are only two structures that are predicted to be more stable than the reactants in the whole free energy surface of the Gewald reaction: Knoevenagel-Cope condensation intermediate **5**, and thiophene product **6**. All polysulfide intermediates are expected to be in equilibrium and interchange using various mechanisms, forming a complex mixture. As such, our calculations indicate that the Gewald reaction is under thermodynamic control: while all polysulfides can interconvert and potentially form cyclic products, only the cyclization of the monosulfide **5b-S^-** produces a stable aromatic product that funnels all intermediates toward 2-aminothiophene **6**.

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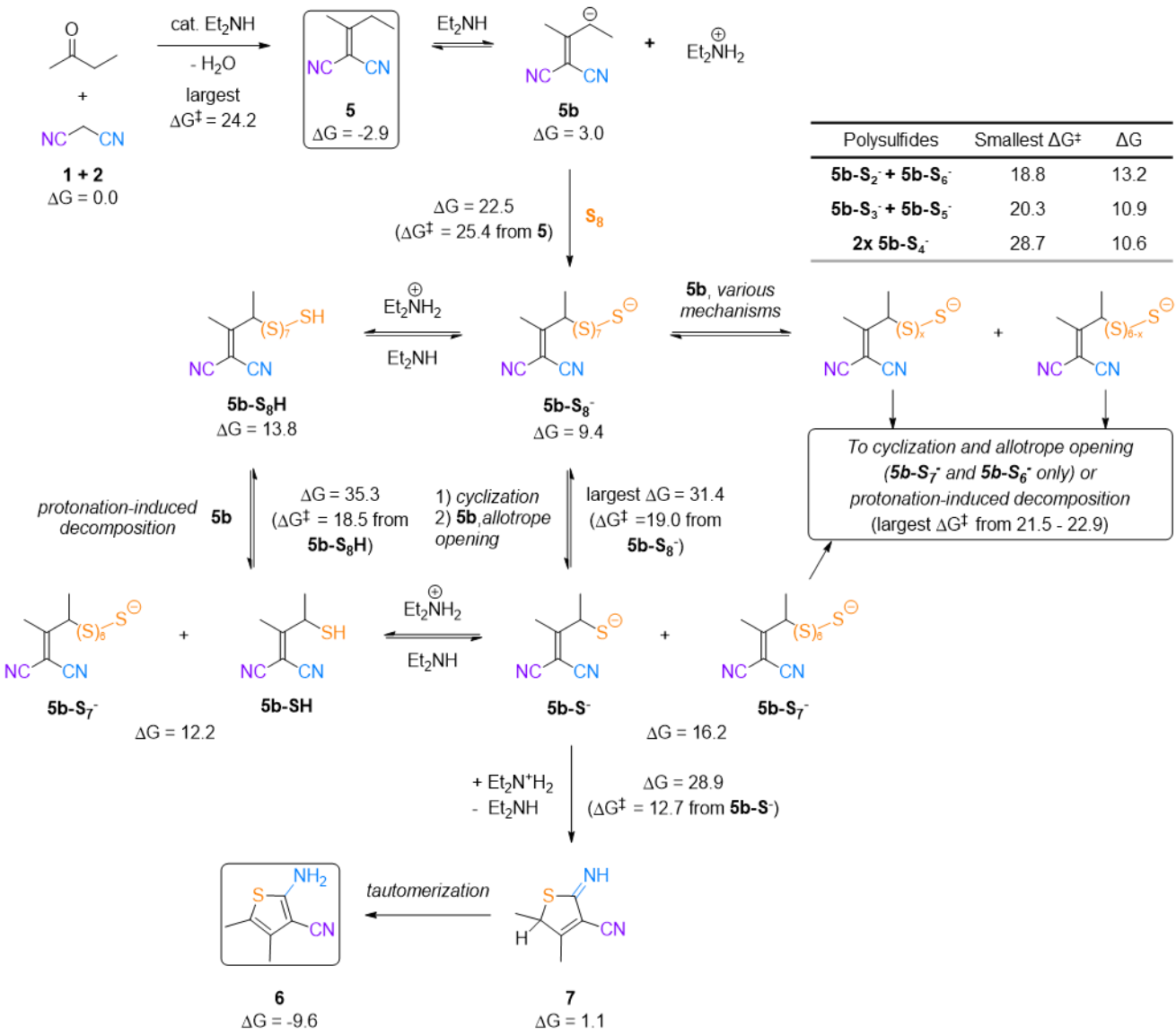

Figure 10: Plausible reaction pathway for Gewald reaction (version II)

Conclusion

Through an extensive Density Functional Theory (DFT) study, a comprehensive investigation of the Gewald reaction was carried out. Our initial findings indicate that amine nucleophiles are unlikely to open elemental sulfur unless at elevated temperatures. Instead, the role of the amine in this reaction is as an acid/base catalyst. Furthermore, our calculations have revealed that the enolate anion of the ketone reagent

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also does not contribute to the sulfur ring opening. As a result, we conclude that the Knoevenagel-Cope condensation serves as the first step in the Gewald reaction. Following the condensation step, the elemental sulfur opening occurs through the deprotonation of the Knoevenagel-Cope product by the base, leading to the formation of the octasulfide intermediate. Several pathways have been investigated to understand the degradation of this octasulfide and shorter polysulfides. Based on our analysis, it was concluded that bimolecular decomposition is only competitive if the polysulfide is protonated. Unimolecular decomposition is kinetically preferred for longer polysulfides (6 and more sulfurs), but none of the proposed pathways provide any thermodynamic driving force and polysulfides of various lengths are expected to coexist in a complex equilibrium. The only thermodynamic driving force in this reaction is the formation of the final 2-aminothiophene product, which happens with a small barrier from the monosulfide intermediate and is highly exergonic, ensuring irreversibility. In summary, our thorough DFT study provides information about the complex processes involved in the Gewald reaction, demonstrating that it is under thermodynamic and not kinetic control. Other reactions involving elemental sulfur and carbon nucleophiles, especially where there are no functional groups that would stabilize certain polysulfides over others, are likely to follow similar rules. Our work can serve as a starting point for further mechanistic studies of reactions involving elemental sulfur, which are sure to uncover more intricacies about polysulfides and their reactivity.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information files.

Supporting Information.

Computational details, additional figures and tables, energies and XYZ coordinates of all computed structures. Gaussian 16 output files and XYZ files for all computed structures.

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Author Contributions

The manuscript was written through contributions of all authors. JS and PAC performed and analyzed the calculations.

Conflicts of Interest

No conflicts to declare.

ACKNOWLEDGMENT

This work was supported by the donors of the ACS Petroleum Research Fund under Doctoral New Investigator Grant 61891-DNI4.Calculations for this study were performed on the Lochness and Wulver clusters at NJIT and the support of the High-Performance Computing team is gratefully acknowledged.

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